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Signed Andrew Gersey

Dated **6 March 2000**

Patents Form 1/77

Patents Act 1977
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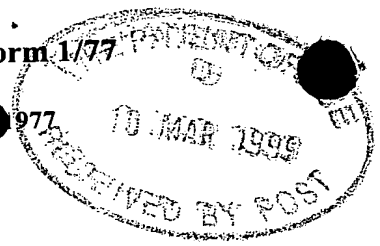


**The Patent Office**

10 MAR 1999

**1/77**

11MAR99 E431686-1 D02029
P01/7700 0.00 - 9905512.1

# Request for grant of a patent

*(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*

**The Patent Office**
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — DMW/NM/P32266

2. Patent application number
*(The Patent Office will fill in his part)* — **9905512.1**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

SmithKline Beecham plc
New Horizons Court, Brentford, Middx TW8 9EP,
Great Britain

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — S2009749002

4. Title of the invention — Process

5. Name of your agent *(if you have one)*

CORPORATE INTELLECTUAL PROPERTY

"Address for service" in the United Kingdom to which all correspondence should be sent
*(including the postcode)*

SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

Patents ADP number *(if you know it)* — S2009749004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day / month / year)* |
|---|---|

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

*a) any applicant named in part 3 is not an inventor, or*
*b) there is an inventor who is named as an applicant, or*
*c) any named applicant is a corporate body*
*See note (d)*

9. Enter the number of sheets for [redacted] of the following items you are filing with this form. Do not count copies of the same document

| | |
|---|---|
| Continuation sheets of this form | 1 |
| Description | 4 |
| Claim(s) | 1 |
| Abstract | |
| Drawings | 4 |

10. If you are also filing any of the following, state how many against each item.

| | |
|---|---|
| Priority Documents | |
| Translations of priority documents | |
| Statement of inventorship and right to grant of a patent *(Patents Form 1/77)* | |
| Request for preliminary examination and search *(Patents Form 9/77)* | |
| Request for substantive examination *(Patents Form 10/77)* | |
| Any other documents *(please specify)* | |

11. We request the grant of a patent on the basis of this application
Signature _____ Date 9-Mar-99
D M Waters

12. Name and daytime telephone number of person to contact in the United Kingdom — D M Waters 01279 644283

**Warning**

*After an application for a Patent has beeen filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.*

**Notes**

*a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505*
*b) Write your answers in capital letters using black ink or you may type them.*
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**Process**

The present invention relates to a process for the crystallisation of a substance, and more particularly a substance to be used as a pharmaceutical.

Crystallisation is a well known technique for the purification of chemical compounds. Crystalline products prepared using traditional batch methodology may vary; for example in the degree of agglomeration experienced and the habit and size of individual crystals so formed. It would be particularly advantageous if crystallisation could be carried out as a continuous process to access the desirable benefits of fast crystallisation processes, especially products of uniform and consistently small crystal size; without the problems of batch processing, especially oiling or solvent inclusion. This is particularly true for pharmaceutically active compounds which might have to be milled to improve their bioavailability, or to increase their suitability in processing, e.g. the electrostatic deposition of active ingredients in tablet manufacture.

According to the invention there is provided a process for the continuous crystallisation of a chemical compound which comprises contacting a stream of either the compound or a salt thereof dissolved in a solvent with a stream of colder solvent or anti-solvent, or a solution of an appropriate acid or base, and separating off the crystals formed. Preferably the solute/solvent/antisolvent system will be one which has a fast precipitation time. By 'precipitation time', we mean the time taken to observe precipitation in a mixed system e.g. cloudiness. Precipitation times can be determined by mixing and observing precipitation in individual solvent systems. Preferably the precipitation time will be less than 1 minute, especially less than 5 seconds, and particularly less than 1 second. Precipitation times can be varied by adjusting the concentration of solute, the rates of flow of solution and antisolvent, and the temperatures of the solvent and antisolvent.

It should be recognised that the process of crystallisation can involve the initial formation of amorphous solid particles which rapidly change into a crystalline form.

Preferably the contacting process is undertaken using conditions of high shear and turbulence, and particularly preferably under controlled residence times in a vortex mixer. Controlled residence times in the mixer give a product of uniform crystal size and fast precipitation times give particularly small crystals.

One advantage of the process is that the use of rapid intense mixing allows the process to be used under conditions where conventional batch mode crystallisation wither does not work or gives poor results, i.e. the use of conditions of fast

precipitation without turbulent mixing usually gives oils or crystal containing occluded impurities.

Mixing devices suitable for use in this invention include known in-line mixers, e.g. of the type in which one or more turbulence-creating elements are located within a pipeline through which the components are caused to flow. Another suitable type of mixer is a homogeniser, e.g. of the type in which two liquid phases are forced under pressure through a biased valve. Suitable mixing devices may also include cavities subjected to high turbulence and or shear stress by means of turbines, propellers etc.

Another and preferred type of mixer is a chamber wherein introduced fluids are subjected to intense rotational swirling, for example a vortex chamber of the type disclosed generally in EP-0153843-A (UK Atomic Energy Authority, the contents of which are incorporated herein by reference), the vortex chamber comprising a chamber of substantially circular cross section, e.g. generally cylindrical in shape, and having tangential inlets and an axial outlet. In such a mixer, the components are introduced via the tangential inlets where they experience swirling and intense mixing as they radially accelerate towards the centrally located outlet.

Preferably a vortex mixer (e.g. a Power Fluidics mixer) is used to create the conditions of high shear and turbulence; however, a simple 'Y'-connection may prove satisfactory for many applications provided that appropriate flowrates are used.

Preferably the mixed stream of solute in solvent and antisolvent is cooled during the mixing process and/or subsequent to it before the crystalline material is separated from the solvent stream. Optionally one or more tubular reactors are introduced before the crystals are separated off; optionally such tubular reactors are cooled.

Preferably the compound to be crystallised is an active ingredient for a pharmaceutical composition.

Preferably the process is one in which the compound crystallised is the same salt form as the compound in the solvent added to the antisolvent (i.e. free base, acid-addition salt or base-addition salt). However the process can be used where a solution containing the free base of a compound is mixed under conditions of high turbulence with a solvent containing an acid or base, or alternatively where a solution of a salt of a compound is rapidly mixed under conditions of high turbulence with a solvent containing an acid or base.

A preferred compound for crystallisation is eprosartan methanesulphonate ((E)-[[2-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene]-2-thiophene propanoic acid methanesulphonate) which is described in U.S. 5,185,351/EP 0 403 159. Preferably the crystallised eprosartan methanesulphonate has a $d_{90}$ of less than 10 microns.

Preferably the solution of the solute is a solution of eprosartan mesylate in acetic acid, preferably at an elevated temperature for example from 20°C to 100°C, preferably 70°C to 90°C and especially between 75-85°C.

Preferably the solution of the solute is reasonably concentrated, for example between 5 and 40% w/v, preferably between 10 and 30% w/v and especially between 15% and 25% w/v.

Preferably the antisolvent is ethyl acetate or tert-butyl methyl ether (TBME), especially TBME. Preferably the antisolvent is used in a significant excess to the solution of solute, for example from a 3-fold to a 30-fold excess, preferably 6:1 to 25:1.

Preferably the antisolvent is mixed at a temperature from -20°C to 80°C, preferably 0°C to 30°C, particularly preferably around 10 °C to 20°C.

We have found that using a solution of eprosartan methanesulphonate dissolved in hot acetic acid and an antisolvent of tert-butyl methyl ether at around 20°C, that crystals of a particularly advantageous small and uniform size and consistency are obtained.

The invention will now be described by way of example only with reference to the accompanying drawings, in which:
Fig 1 shows a mixing device in the form of a vortex chamber having two tangential inlets and an axial outlet.
The vortex chamber consists of an essentially cylindrical chamber, having two tangential inlets. The internal diameter of the vortex chamber is about 8 mm, and its height about 1mm.

Vortex mixer technology is used to effectively mix two inlet streams in a vortex environment to control crystal growth. Each stream is fed at high velocity into the central mixing chamber where it is mixed and accelerated towards to the central exit orifice. A combination of small mixing chamber volume (approx. 0.1ml) and high

throughputs (preferably between 0.5L and 2L/min) generate typical residence time of less than 10ms in a steady-state environment where all elements of the mixed stream experience minimal forward and backmixing. This effectively fixes supersaturation levels within the device with resultant tight control of particle size. By contrast, local supersaturation levels will typically occur in a conventional batch stirred reactor due to non-ideal mixing behaviour and both axial and radial heat gradients throughout the system. Eprosartan methanesulphonate prepared by reactive crystallisation of the free base with methanesulphonic acid has a broad distribution - fig 2 shows material thus prepared. Optionally tubular reactors are introduced after the mixing chamber and before separation of the crystalline material.

Particle size distributions were found to be narrow, uni-modal and near symmetrical with $d_{10}$, $d_{50}$ and $d_{90}$ values of 1, 3.5 and 7 micron respectively (figs 3 & 4). There is good demonstrated good reproducibility with no observed agglomeration. By comparison, the slow controlled addition of eprosartan mesylate/acetic acid solution to excess tert-butyl methyl ether with vigorous stirring in a semi-batch mode environment without use of a vortex mixer leads to a much broader size distribution of the generated particles (fig. 4).

Claims:

1. A process for the continuous crystallisation of a chemical compound which comprises contacting a stream of either the compound or a salt thereof dissolved in a solvent with a stream of colder solvent or anti-solvent, or a solution of an appropriate acid or base, and separating off the crystals formed.

2. A process according to Claim 1 in which the contacting process is undertaken using conditions of high shear and turbulence.

3. A process according to Claims 1 or 2 in which the solute/solvent/antisolvent system has a precipitation time of less than 5 seconds.

4. A process according to any one of Claims 1 to 3 in which a vortex mixer or Y-connection is used to effect mixing.

5. A process according to any one of Claims 1 to 4 in which the compound is not converted into a different salt form.

6. A process according to any one of Claims 1 to 5 in which the compound is eprosartan methanesulphonate using acetic acid as solvent and tert-butyl methyl ether as antisolvent.

7. A process according to any one of Claims 1 to 6 in which the compound to be crystallised is an active ingredient for a pharmaceutical composition.

8. A crystalline compound having small and uniform crystal size prepared by a process according to any one of Claims 1 to 7.

9. Crystalline eprosartan mesylate with a $d_{90}$ value of less than 10 micron.

# The Vortex Mixer

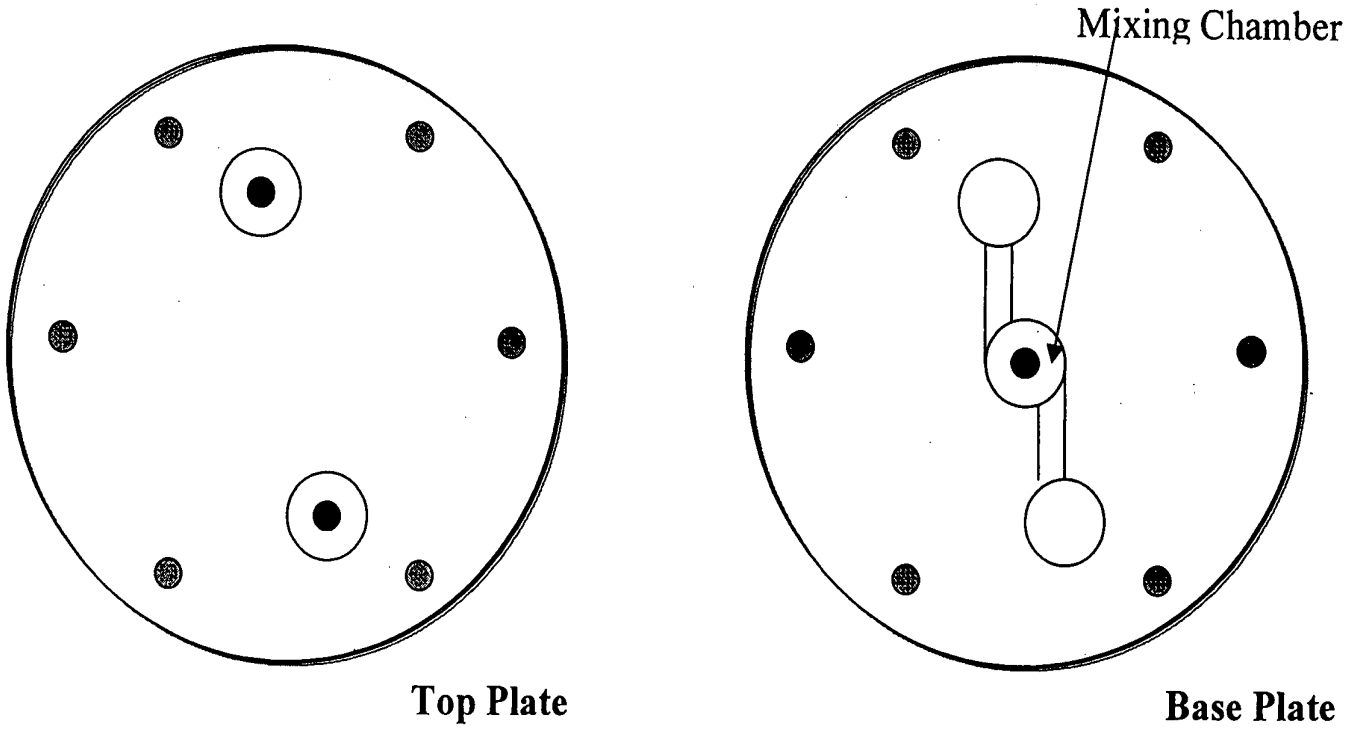


**Fig 1**

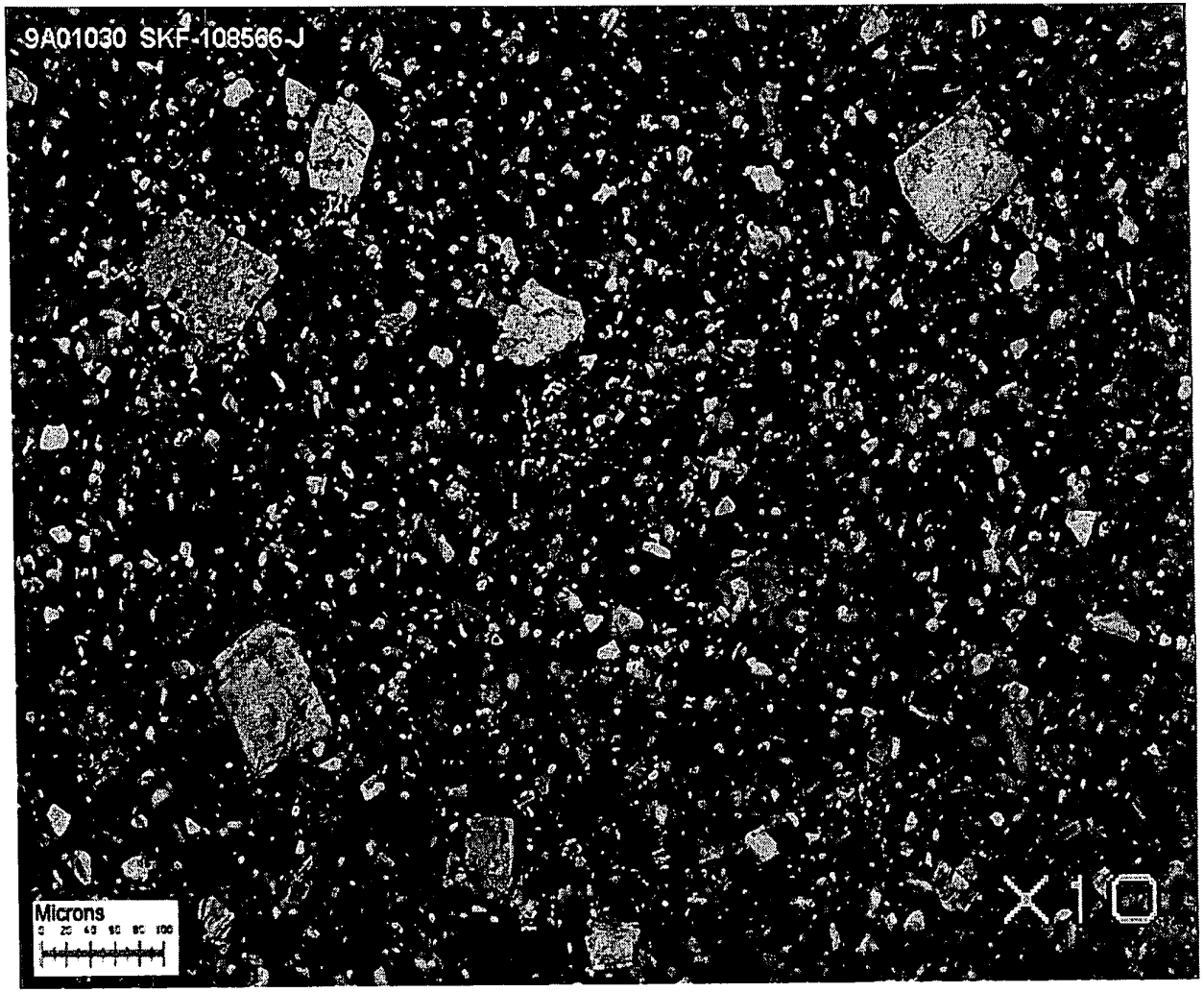


Fig 2

Crystals of eprosartan methanesulphonate obtained by batch crystallisation

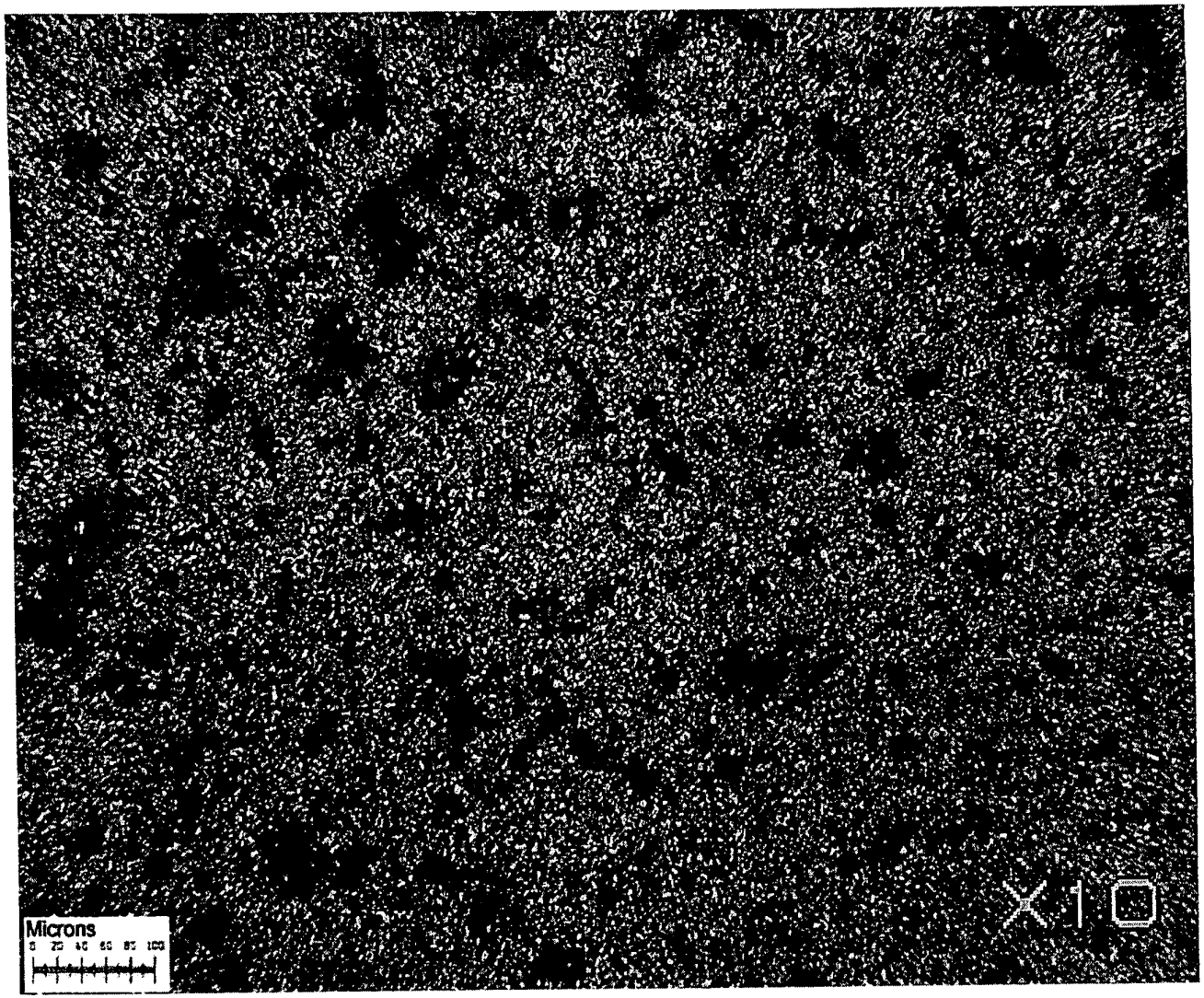


**Fig 3**

**Crystals of eprosartan methanesulphonate produced by continuous crystallisation using a vortex mixer**

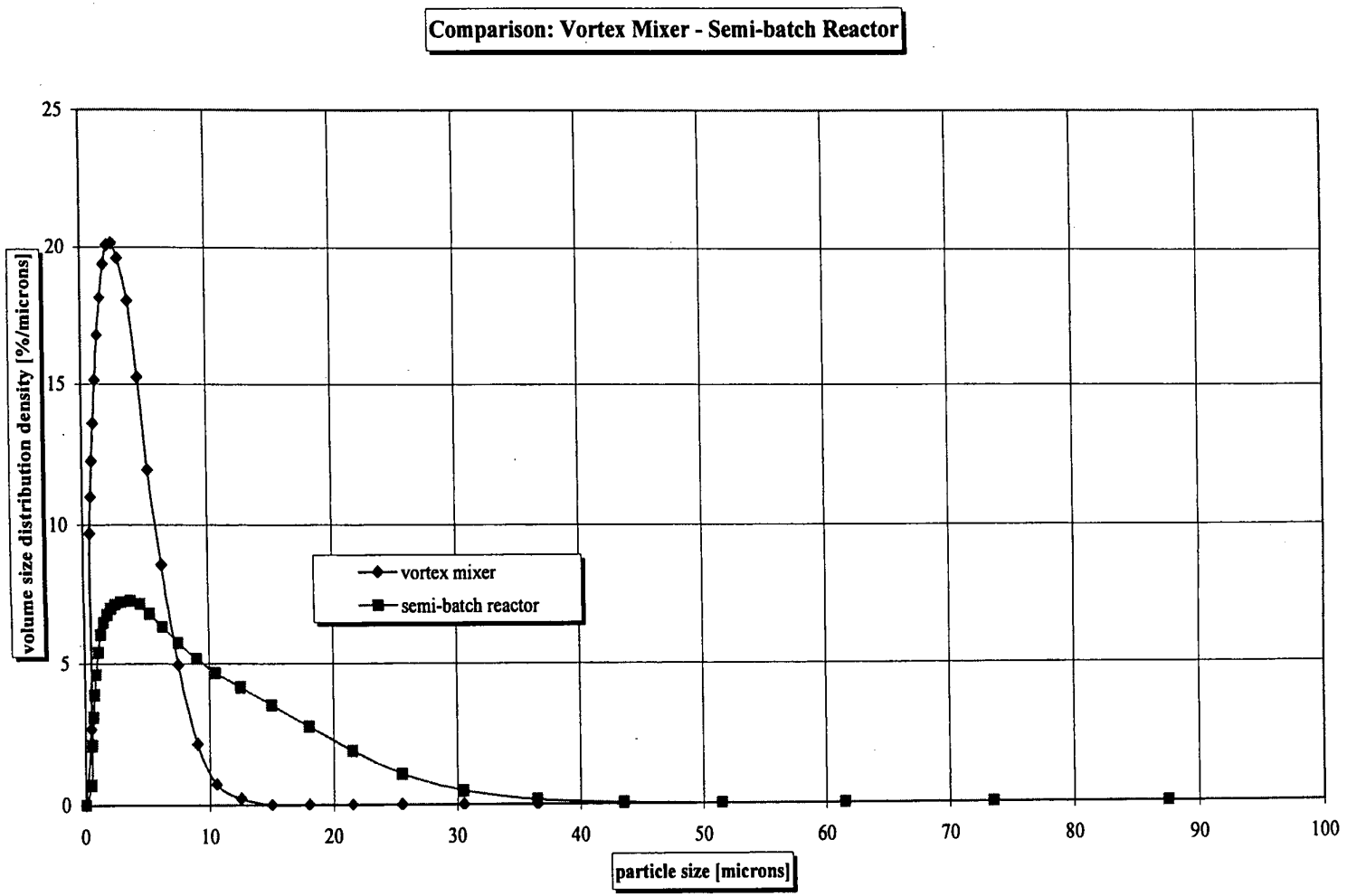
Comparison: Vortex Mixer - Semi-batch Reactor
volume size distribution density [%/microns]
25
20
15
10
5
0
vortex mixer
semi-batch reactor
0
10
20
30
40
50
60
70
80
90
100
particle size [microns]

Fig. 4